Adrenal Fatigue

Enhancing Quality of Life for Patients with a Functional Disorder

Chris D. Meletis, N.D., and
Wayne A. Centrone, N.D., A.T.-C.

The human organism is bombarded with an incredible variety of stresses at any given time. Stress can be categorized in an equally dizzying number of ways. There are both chronic and acute stressors. There are somatic stressors that push the body away from homeostasis. There are psychogenic stressors that seem to be triggered at the slightest provocation. An elaborate system of hormones and neurotransmitters (coupled with the human penchant for becoming upset about nonphysical stressors) engenders psychogenic stress in human beings more than in any other species of animal.*

There are two basic kinds of psychogenic stress (1) rational (fear) and (2) irrational (anxiety). Regardless of the nature of the stress—mental or physical, rational or irrational—the body responds to all stress in a fairly predictable manner. In the early 1930s, Selye[1] termed this predictable pattern of response the general adaptation syndrome.

Both conventional and nutritionally oriented health care providers principally utilize and share the same biomedical model of stress and its physiologic effects. However, the two schools of practice diverge when it comes to diagnostic methodologies that are used to identify subclinical cases of adrenal dysfunction and the modalities used to treat these patients.

How the Adrenal Glands Respond to Stress

At the center of the stress response are the adrenal glands. The adrenals produce epinephrine and norepinephrine, along with other hormones such as cortisol that enable the body to adapt to and survive a stressor. The acute alarm, or immediate reaction to a stressor, is a physiologic phenomenon in which the sympathetic nervous system responds to exogenous or endogenous stressors put the body into what is popularly called the "fight, fright, or flight" mode. When the body is in this state, such as in potentially life-threatening situations, adrenal hormones are released to increase heart rate and blood pressure and divert blood to the brain, heart, and skeletal muscles. This physiologic compensation is a key mechanism in stress and the clinical phenomenon of adrenal fatigue.

The adrenal cortex produces steroid hormones, which include cortisone, hydrocortisone, testosterone, estrogen, 17-hydroxyketosteroids, dehydroepiandrosterone (DHEA), DHEA sulfate, pregnenolone, aldosterone, androstenedione, progesterone, and other intermediates to hormone production. These are the most widely studied of the stress-related hormones. Although most of these hormones are created in different parts of the body, aldosterone, cortisone, and hydrocortisone are produced only in the adrenal glands.

Aldosterone, working in cooperation with the renal system, helps to regulate the balance of sodium and potassium in the body. This regulation is critical to many physiologic functions, including the ability to react to stress and to maintain fluid balance. This hormone also contributes to the maintenance of blood pressure. In "adrenal fatigue" states, patients may have alterations in the fluid-balancing mechanism., with the most commonly described symptom being "puffy hands and feet."

Recent conventional medical research has shown that subclinical adrenocortical disease can exist without adrenal function failure.[2] The etiology of this subclinical disease process has not been elucidated fully in conservative research. Authors who write for alternative medical periodicals and texts have historically expressed a belief that severe, long-term stress can lead to a clinical phenomenon known as "adrenal burnout."[3,4]

Most individuals adapt to the stresses of life and, when these stressors are reduced, these patients experience favorable psychophysiologic responses, demonstrating the correlation between stress and physiologic functioning.[5] Being unable to adapt to stressors can manifest as "staleness syndrome" or adrenal dysfunction.[3,4,6] Individuals who experience this disorder are unable to perform at their customary levels of activity at the office or home. They seem to suffer from persistent deterioration in their everyday functioning and activities. Indeed, depression and a marked decrease in performance seem to be the hallmark of this maladaptation syndrome.[7,8]

Biochemical Reactions to Stressors

The fight, fright, or flight response to stressors involves the catecholamines, substances that prepare the body for a call to immediate action and response, by causing short-term hyperglycemia. This rapid catabolism of blood glucose is the result of liver-glycogen storage breakdown and an increased rate of gluconeogenesis. Catecholamines can also liberate rapid stores of energy by catabolizing fat from adipose tissue stores.

*Sapolsky R. Stress and disease: Who gets sick and who stays well. Institute for CorTexT Research and Development, Stanford University, Department of Biological Sciences and Neuroscience. Spring 1995 lecture.

Botanicals for Treating Adrenocortical Dysfunction

Botanical agent	R_X	Mechanism of action
Licorice (*Glycyrrhiza glabra*)	1–2 g per day (can go as high as 30 g)	Suppresses 5-β-reductase activity; may cause blood pressure elevations requiring monitoring
Hog weed (*Boerhaavia diffusa*)	Unknown	Buffers plasma cortisol elevation; reverses adrenal cortisol depletion under high levels of stress
Ashwagana (*Withania somnifera*)	10–60 drops tid–q.i.d of fresh plant-liquid extract[a]	Glucocorticoid-like effects from plant sterols
Siberian ginseng (*Eleutherococcus senticosus*)	Dry strength liquid extract: 20–60 drops q.d.–q.i.d[a]	Binds to mineral- and glucocorticoid-receptors

[a]Tilgner S. Herbal Medicine: From the Heart of the Earth. Cottage Grove, OR: Wise Acres Press, 1999.

The stress adaptation phase primarily involves glucocorticoids, released by the adrenal cortex, that have a profound effect on energy metabolism and biologic functions. These substances raise blood-sugar levels, increase muscle-protein breakdown and hepatic gluconeogenesis, and mobilize fatty acids.[9] Following normal diurnal patterns for the release of serum cortisol, glucocorticoid levels are at their lowest point at approximately midnight to 1 AM. Peak levels occur between 6 AM and 8 AM. Research has shown that elevation or suppression of daily cortisol levels indicates imbalanced hepatic–pituitary–axis (HPA) activity.[10] This may be interpreted as hyperfunction or hypofunction, depending on a patient's levels of cortisol and his or her clinical presentation.

Sustained activation of the sympathetic nervous system marks the compensation stage, also known as the adrenal hyperfunction stage, with a secondary influence on the HPA axis. The pituitary gland responds to the influence of sympathetic nervous system activity by releasing adrenocorticotropic hormone (ACTH). In turn, the adrenal glands respond to the pituitary release of ACTH by producing excess cortisol and androgen hormones.

In an attempt to compensate for this faulty hyperfunction, the hypothalamus–pituitary axis becomes less sensitive to the influence of cortisol's feedback inhibition. As serum cortisol levels rise, glucose utilization declines and insulin resistance increases, gluconeogenesis in the liver increases, and blood glucose levels increase rapidly. In addition, the body responds to increased cortisol by increasing the degradation of protein stores to supply amino acids for gluconeogenesis in an attempt to mobilize energy rapidly.

Adrenal hyperfunction can be marked by a tendency toward insulin resistance, hypertension, mild obesity, and elevated serum lipid and triglyceride levels. What is more, high cortisol and lowered DHEA have been shown to suppress the immune system.[11] Histologic studies have revealed lowered production of secretory immunoglobulin A (sIgA) in the mucus membranes of competition swimmers under the influence of chronic levels of physiologic and psychologic stressors. At this phase of the stress response, athletes and other individuals will often complain of a decrease in performance or work production and a generalized feeling of lassitude.

The final stage of the stress response is the adrenal hypofunction stage or the fatigue stage. The body's ability to synthesize cortisol and other corticosteroid hormones is greatly diminished. The resulting excessive fatigue, changes in a person's ability to concentrate, inability to tolerate alcohol, intractable headaches, lowered blood pressure, menstrual irregularities, reactive hypoglycemia, and carbohydrate sensitivity may follow.[12] With this compromised ability to control inflammation, the body goes into a proinflammatory state. The absence of cortisol leads to an increase in endogenous inflammatory eicosanoids and cytokines and leads to eventual tissue damage and degenerative disease.[13]

Effects of Stress on the Body

We often hear of 30-year-old marathon runners who are forced into early retirement because of recalcitrant tendonitis. Are these simply cases of poor biomechanics and faulty training plans? Or are these athletes suffering from a maladaptation syndrome in which their bodies can no longer compensate for massive levels of exogenous and endogenous stress (work, family responsibilities, exercise, etc.)? Uncontrolled stress strains the entire organism. Stress increases the metabolic rate, resulting in the mobilization of stored energy sources and the eventual breakdown of muscle protein to make up for energy shortfalls.[14] In short, the body attempts to maintain homeostasis at all costs.

Extended bouts of stress, such as high-volume exercise, psychologic stress, or other lifestyle challenges, lead to abnormal increases in serum cortisol levels and irregular circadian rhythm variations in cortisol secretion.[15] Sustained elevated levels of cortisol may lead to reduced adrenal responsiveness to ACTH.[16] This is compensated for by increases in pituitary releases of ACTH in the initial stages of overtraining. However, protracted stress causes pituitary release of ACTH to decrease and, thus, the pituitary gland becomes underresponsive to stimulation. The ultimate effects of prolonged elevated levels of cortisol are suppression of corticotropin-releasing hormone and ACTH release and atrophy of the zonae fasciculata and reticularis as a consequence of ACTH deficiency.[17] Finally, the HPA axis fails to respond to stress and stimulation.[18] This clinical measurement of suppressed endocrine function may be the defining element in the accurate identification and appropriate treatment of chronic "overstress syndrome."[19]

Overuse of Corticosteroids

Cortisone and hydrocortisone help to regulate the body's glucose. Since the late 1940s, corticosteroids have been used medically to alter and suppress immune function. With a phenomenal range of applications, corticosteroids were quickly adopted as "miracle cures" for the full range of autoimmune diseases,

including the difficult-to-manage rheumatoid arthritis. However, it did not take long for clinicians and researchers to discover that there was a severe cost for chronic corticosteroid use. Countless patients developed physical conditions that prior to such widespread use of these agents were rarely seen by practitioners of Western medicine. Cushing's syndrome, an overt hypercortisolemia disease, became the price a patient paid for poorly monitored corticosteroid administration.

Diagnosing Adrenal Dysfunction

The fine homeostatic balance between health and disease can be disturbed if the clinical cause of a patient's original imbalance is not fully explored and treated. Indeed, replacement or augmentation of hormones from exogenous sources, all too often, merely suppresses symptoms while leaving the underlying disease process to advance without the diagnostically helpful symptoms.

When addressing adrenal imbalance, it is essential to look beyond laboratory tests and symptoms alone and to integrate the clinical presentation as a whole. Just as overt signs and symptoms of thyroid dysfunction may or may not always manifest with abnormal laboratory tests, a functional adrenal condition may be present in the absence of abnormal laboratory findings. In fact, a recent plethora of medical literature points to the seemingly error-prone assessment that results from measuring thyroid function solely via laboratory tests.

The main cause of adrenal fatigue is continual low-level stress, which taxes the adrenal glands, limiting their ability to adapt to acute stressors. This low-level stress may be caused by emotional or physical upsets or loss of sleep. Clinically, this manifests in the development of exhaustion that does not become resolved with standard rest and relaxation.

A large number of symptoms associated with adrenal dysfunction have been reported in the literature. These symptoms are often categorized according to physiologic performance, psychologic/information processing, and immunologic and biochemical parameters.[20] To date, however, there is no universally agreed-on group of symptoms that describes accurately the condition or the physiologic/psychologic/emotional distresses that some people experience. Rather, multiple symptoms may present in no particular combination under the general categories of adrenal exhaustion, hypoadrenocorticalism, and hyperadrenocorticalism.

Perhaps the most confusing and controversial clinical component of diagnosing and treating adrenal imbalance is codifying the testing parameters to determine conclusively the presence of adrenal exhaustion and dysfunction.

To advance alternative medicine in evidence-based clinical practice, tools must be developed that can give practitioners a comprehensive approach diagnosing adrenal burnout syndrome. By combining biochemical studies, endocrine assays, and physiologic functioning tests, these assessment methods would allow a clinician to gain a greater understanding of a patient's stress response. Numerous assessment methods have been proposed and are utilized to measure and track adrenal dysfunction. Some of these testing models are listed below.

The 24-Hour Salivary Cortisol Pattern

This pattern consists of four points—7 AM–8 AM, noon, 4 PM–5 PM, and 11 PM–midnight. Research suggests that measuring salivary, as opposed to serum cortisol and DHEA, levels may be the best indication of adrenal function.[21–24] Yet controversy exists concerning the complete validity of such testing methods because of potentially confounding variables, such as dietary interference, diurnal variations in salivary pro-

Nutraceuticals for Treating Adrenocortical Dysfunction

Nutraceutical	R_X	Mechanism of action
Vitamin C	1000 mg, 3 times per day	Acts as a reducing agent for the mixed function oxidase used in the synthesis of steroid hormones[a]
Pantothenic acid	500 mg, 2 times per day	Increases corticosteroid production and normalizes response to ACTH[b]
Vitamin B complex	50–100 mg per day	Helps to transfer methyl groups and regenerate methionine
Seriphos™ (PS)	500 mg 2 times per day, 15 minutes prior to eating	Orally, prescribed PS product has decreased plasma cortisol and ACTH levels in healthy research subjects[c]
Magnesium	150 mg, 3 times per day	A cofactor for most ATP-dependent reactions and activation of intracellular secondary messenger cAMP
Zinc	15 mg, 2 times per day, with food	Zinc deficiency increases membrane susceptibility to oxygen free-radical damage
α-lipoic acid	150 mg, 3 times per day	Cofactor for the citric-acid cycle; potent antioxidant; partially restores the hydrocortisone suppression of T-helper cell activity[d]
Adrenal glandular support	400–500 mg per day or as directed by manufacturer	Unknown; further research is needed

[a]Kodama M, Inoue F, Kodama T. Intraperitoneal administration of ascorbic acid delays the turnover of labeled cortisol in plasma of ODA rat, but not Wistar rat: Evidence in support of the cardinal role of vitamin C in the progression of glucocorticoid synthesis. In Vivo 1996;10:97–110; [b]Pietrzik K, Ginta E. Response of hepatitis drug–metabolizing enzymes to immobilization stress in rats of various ages. Acta Physiol Hungarica 1993;81:29–35; [c]Monteleone P, Maj M, Beinert L, et al. Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo–pituitary–adrenal axis in healthy men. Eur J Clin Pharmacol 1992;41:385–388; [d]Ohmori H, Yamauchi T, Yamamoto I. Augmentation of the antibody response by lipoic acid in mice. Jpn J Pharmacol 1986;42:275–280.

ACTH, adrenocoricotropic hormone; ATP, adenosine triphosphate; cAMP, cyclic adensosine monophosphate; PS, phosphatidyl serine.

duction and viscosity, oral contaminants, and the potential presence of gingival disease or problems regarding the mouth ecology.

The 24-Hour Urine Free-Hormone Profiles

ACTHs are part of a complex pathway of biochemical messengers. It is, therefore, difficult to identify where, exactly, in this "pathway" dysfunction may be occurring. In response to this complexity, comprehensive testing laboratories have developed methods for evaluating primary and secondary steroid hormones and their most important metabolites. This provides practitioners with a tool to examine the stress response more fully in the context of overall hormonal balance including precursors and metabolites of the hormones.[25]

sIgA

A protein modulator of immune activity, sIgA is intimately linked to the activity of the autonomic nervous system. Alterations and dysfunctions in the autonomic nervous system can be measured directly by changes in salivary composition and excretion. Medical researchers have recently theorized that factors such as exercise and chronic stress might induce changes in several components of saliva, such as immunoglobulins and proteins.

To compensate for increased stressors, many individuals have turned to ergogenic or energy enhancement substances.

Plasma Glutamine

Glutamine is considered to be a conditionally essential amino acid because it can be synthesized in the body from glutamic acid. Glutamine is an important modulator of many homeostatic functions and optimal functioning of specialized tissues within the body. These tissues are key to gut and immune system function. Researchers have recognized certain conditions in which the body's demand for glutamine exceeds its ability to synthesize it. Such conditions are associated with high levels of physiologic stress. Under such chronic, catabolic conditions, the body takes its supply of glutamine from muscle tissue.[26]

Total Blood Cholesterol

Researchers theorize that because the body alters its ability to compensate for a shift in adrenal function, stress has a deleterious influence on cholesterol synthesis and specific lipoprotein molecules. Measuring total body cholesterol will allow researchers to correlate changes in adrenal function with shifts in cholesterol levels.

Serum Ferritin

Ferritin reflects the body's iron stores and is a good indicator of iron storage status. The ferritin test is more sensitive than the iron or total iron binding capacity test for diagnosing iron deficiency or overload. Measuring ferritin levels will provide an additional means of assessing immune function and physiologic adaptation to stress.

Morning Basal Body Temperature

Cortisol has a profound suppressive effect on thyroid-axis function. In the presence of elevated cortisol, thyroid functioning can become significantly impaired. The resultant changes in thyroid metabolism can include suppression of thyroid-stimulating hormone (thyrotropin; TSH) and decreased conversion of thyroid hormone from thyroxine (T_4) to the more potent form of triiodothyronine (T_3) in peripheral tissues. It has been hypothesized that these effects arise from inhibition of the enzyme 5-deiodinase, affecting the T_4-to-T_3 conversion and suppression of TSH by endogenous somatostatin.

Postural Muscle Assessment

Research has identified restricted muscular sodium/potassium adenosine triphosphatase (ATPase) activity and reduced cortisol levels in chronically stressed rats. Studies suggest that it is necessary to have an "intact pituitary–adrenal axis for adequate function of the sodium/potassium pump."[27,28] An ion shift with an increased extracellular potassium concentration has also been proposed as a possible cause of muscular complaints during exercise in patients who use β-blockers. Postural muscles (gastrocnemius, soleus, medial hamstrings, short adductors of the thigh, hamstrings, psoas, piriformis, tensor fascia lata quadratus lumborum, erector spinae, latissimus dorsi, upper trapezius, sternomastoid, levator scapulae, pectoralis major, and the flexors of the forearm) shorten under stress. Therefore, evaluation of the postural muscles may be an excellent clinical tool to assess a patient's response to treatment.

Herbal Treatments for Adrenocortical Dysfunction

To compensate for increased stressors, many individuals have turned to ergogenic or energy enhancement substances. These herbal and nutritional supplements are thought to have some type of ergogenic activity and are among the best-selling natural products in nutrition stores, with a financial impact in the $2–3 billion per year range.

Although there is a body of scientific literature on a variety of natural ergogenic substances—such as pyruvate, creatine, ephedra (ma huang; *Ephedra sinica*), ginseng (*Panax* spp.), and guarana (*Paullinia cupana*)—using animal models, there are few well-designed human clinical trials. This paucity of legitimate research, and the high over-the-counter use of natural products suggest an urgent need to conduct studies on the long-term effectiveness and safety of these natural ergogenic aids.

Natural products (such as phytopharmacologic agents), which appear to enhance performance capacity (as demonstrated in animal and human studies), include such nutrients as creatine and pyruvate and such herbs as guarana, ginseng, Siberian ginseng (eleuthero; *Eleutherococcus senticosus*), schisandra (*Schisandra chinensis*), and ashwaganda (*Withania somnifera*).[29–31] Other botani-

cals with purported ergogenic efficacy include regular coffee (*Coffea arabica*), cola nut (*Cola accuminata*), and ephedra. These herbs are thought to have ergogenic effects because they contain methylxanthine compounds (cola nut and coffee beans), which have been shown to mimic the effects of endogenous epinephrine (ephedra). Caffeine, a methylxanthine, has been shown, in human trials, to enhance endurance and exercise performance.[32]

Perhaps the most misunderstood of all adrenal tonic herbs, are the adaptogens. The term adaptogen, coined by Brekhman, was proposed as a more appropriate description for isolated phytochemical compounds. Adaptogens, first identified in 1966 by Brekhman, are, collectively, a group of medically effective substances that put organisms into nonspecific heightened resistance states to help organisms to combat stressors and adapt to extraordinary challenges.

These herbs are of most interest to nutritionally minded physicians as substances that can enhance an individual's resistance to the long-term, cumulative effects of high-volume and high-intensity stress (such as exercise).

Perhaps the most studied of the adaptogenic herbs are Siberian ginseng and licorice (*Glycyrrhiza glabra*). Their purported mechanism of action is to reduce the amount of hydrocortisone broken down by the liver, thereby reducing the workload of the adrenal glands. These herbs were the first to be studied as adaptogens. Additional first-generation adaptogens include schisandra and reishi (*Ganoderma lucidum*). [33]

There are additional botanical agents that have been reported to have adaptogenic qualities but these agents have not been studied extensively for their support of the adrenal system. These include: ashwaganda, gotu kola (*Centella asiatica*), wild oats (*Avena sativa*), astragalus (*huang chi; Astragalus membranaceous*), *fo-ti* or *ho shou wu* (*Polygonum multiflorum*), burdock (*Arctium lappa*), and suma (*Pfaffia paniculata*). There are other herbs that may be classified as adaptogens, but they are not yet fully understood and are not highly available in most Western nations.

In modern scientific research and clinical results, eleuthero is one of the rare herbal medicines that has been tested extensively on humans in clinical trials. Eleuthro's adaptogenic and other protective and strengthening properties have been studied and confirmed with thousands of human volunteers. We can still learn much more about eleuthero, but researchers have already defined some of the ways in which eleuthero affects the body biochemically and have identified certain active constituents that are natural plant steroids, the eleutherosides.

Research has documented that holy basil (*Ocimim sanctum*) acts as an antioxidant and may decrease levels of stress hormones.[34] This herb is a powerful anti-inflammatory that has an effectiveness that is similar to aspirin and ibuprofen. However, unlike aspirin and ibuprofen, this herb is not irritating to the lining of the gastrum. Animal studies have found that holy basil has similar effects to a variety of mood-enhancing pharmaceuticals such as stimulants and antidepressants.

[†]The author has no vested interest in this product.

Botanicals with Purported Adaptogenic Properties

American ginseng (*Panax quinquefolium*)
Ashwaganda (*Withania somnifera*)
Astragalus (*Astragalus membranaceus*) root
Borage (*Borago officinalis*)
Bupleurum (*Bupleurum chinense*)
Cola nut (*Cola nitida*)
Devil's club (*Oplopanax horridum*)
Echinacea (*Echinacea* spp.)
Ginseng (*Panax spp.*)
Licorice (*Glycyrrhiza glabra*)
Oats (*Avena sativa*)
Prickly ash (*Xanthoxylum clava-herculis*) bark
Siberian ginseng (*Eleutherococcus senticosus*)
Scullcap (*Scutellaria lateriflora*)
Suma (*Pfaffia paniculata*)
Turmeric (*Curcuma longa*)

From: Tilgner S. Herbal Medicine: From the Heart of the Earth. OR: Wise Acres Press, 1999.

Nutraceuticals for Treating Adrenocortical Dysfunction

Phosphatidyl serine (PS) is used to treat adrenocortical dysfunction. One product, Seriphos™ (Interplexus, Kent, Washington), provides a form of PS that does not depend on enzyme availability for gastrointestinal-tract absorption.[35,†] This product stimulates neuronal plasticity, acting as a compensatory adaptive mechanism to cell deterioration. PS is also capable of preventing or delaying the age-dependent decline of neurotransmitter function.

Some examples of additional nutritional agents use for treating adrenocortical dysfunction comprehensively include: buffered forms of vitamin C, vitamin B-complex formulas, pantothenic acid, zinc, lipoic acid, and glandular extract supports (also known as protomorphogens or adrenal cortex extracts).

PS is purported to help in optimizing the stress response and repairing the damage wrought by catabolic stress hormones. Clinical studies have demonstrated that subjects experience improvement on computerized and standard neuropsychologic performance tests for sleep and mental function.[35]

The clinically common prescription of PS for optimal absorption, is two capsules (250 mg each) taken before meals (at least 15 minutes before eating) or before bedtime. To mimic the diurnal effect of cortisol, holistic health care practitioners recommend taking two capsules in the morning and two during midafternoon.

Conclusions

A particularly interesting study revealed that cortisol strongly fluctuates with increases and decreases in negative affect. The parameters of this research included testing salivary cortisol levels of 30 healthy young men experiencing an activating and humorous video, a speech stressor, and a resting control. The study researchers found that negative affect increased during the

speech but strongly decreased during the video. The researchers concluded that their results suggested that the HPA axis is a dynamic system that is influenced by changes in negative affect independently of the experience of generalized activation.[36]

An increasing amount of research points to the relation between emotional states and sympathetic nervous system overactivity.[2,37] This research confirms that the mind and body can no longer be looked on as separate moieties. Whatever the underlying mechanism that connects mind and body, the writing on the wall is quite clear—medicine can no longer separate the structure of the human body from the function of the human body. Ultimately, as we have known for a very long time empirically, restoration of homeostasis requires treatment of the whole organism, not just one part of it.[38]

With regard to adrenocortical function, even on the purely physical level, many physicians who practice nutritionally oriented medicine have noted that certain conditions improve with treatment for adrenal fatigue. Some of the more common conditions that respond to this kind of are acute viral illnesses, allergies, gastritis, osteoarthritis, rheumatoid arthritis, eczema, contact dermatitis, urticaria, psoriasis, and allergic rhinitis. □

References

1. Kovacs K, Selye H. The original and creative scientist. Ann NY Acad Sci 1998;851:13–15.
2. Terzolo M, Osella G, Ali A, Borretta G, Cesario F, Paccotti P, Angeli A. Subclinical Cushing's syndrome in adrenal incidentaloma. Clin Endocrinol 1998;48(1):89–97.
3. Tintera JW. Hypoadrenocorticism. Troy, NY: Hypoglycemia Foundation, Inc., 1980.
4. Opstad K. Circadian rhythm of hormones is extinguished during prolonged physical stress, sleep and energy deficiency in young men. Eur J Endocrinol 1994;131:56–66.
5. Ronizo RA. Nutritional support for adrenal function. Am J Nat Med 1998;5:12–17.
6. Morgan WP, Brown DR, Raglin JS, O'Connor PJ, Ellickson KA. Psychological monitoring of overtraining and staleness. Br J Sports Med 1987;21:408–414.
7. Chrousos GP. Stressors, stress, and neuroendocrine Integration of the adaptive response. Ann NY Acad Sci 1998;851:311–356.
8. Szabo S. Hans Selye and the Development of the Stress Concept. Ann NY Acad Sci 1998;851:19–27.
9. Ronzio RA. Nutritional support for adrenal function. Am J Nat Med 1998;5(5):12–17.
10. Kelly GS. Nutritional and botanical interventions to assist with adaptation to stress. Alt Med Rev 1999;4(4):249–265.
11. Gleeson M, McDonald WA, Cripps AW, Pyne DB, Clancy RL, Fricker PA, Wlodarrczyk JH. Exercise, stress, and mucosal immunity in elite athletes. Adv Mucosal Immunol 1995;2:571–574.
12. Smith LL. Cytokine hypothesis of overtraining: A physiological adaptation to excessive stress? Med Sci Sports Exerc 2000;32(2):317–331.
13. Heiderscheit BC, Hamil J, Van Emmerik REA. Q-angle influences on the variability of lower extremity coordination during running. Med Sci Sports Exerc 1999;31(9):1313–1319.
14. Stone D, Green C, Rao U, Aizawa H, Yamaji T, Niyibizi C, Carlin G, Woo SL. Cytokine-induced tendinitis: A preliminary study in rabbits. J Orthoped Res 999; 17(2):168–177.
15. Kreider RB, Fry AC, O'Toole ML. Overtraining in Sport. Champaign, IL: Human Kinetics, 1988.
16. Lehmann M, Foster C, Hans-Harmann D, Gastman U. Autonomic imbalance hypothesis and overtraining syndrome. Med Sci Sports Exerc 1998;30(7):1140–1145.
17. Demitrack MA, Crofford LJ. Evidence for the pathophysiological implications of hypothalamic–pituitary–adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann NY Acad Sci 1998;840(4):684–697.
18. Greenspan FS, Strewler GJ. Basic and Clinical Endocrinology. Stamford, CT: Appleton and Lange/Simon & Schuster, 1997.
19. Fry RW, Morton AR, Garcia-Webb P, Crawford GPM, Keast D. Biological responses to overload training in endurance sports. Eur J Appl Physiol 1992;64:335–344.
20. Marsden P, McCullagh AG. Endocrinology: Management of Common Diseases in Family Practice. Lancaster, England. PSG Publishing, 1985.
21. Lac G, Lac N, Robert A. Steroid assays in saliva: A method to detect plasmatic contaminations. Arch Int Physiol Biochem 1993;101:257–262.
22. Vining RF, McGinley RA. The measurement of hormones in saliva: Possibilities and pitfalls. J Steroid Biochem 1987;27:81–94.
23. Tunn S, Möllmann H, Barth J, Derendorf H, Krieg M. Simultaneous measurement of cortisol in serum and saliva after different forms of cortisol administration. Clin Chem 1992;38:1491–1494.
24. Peters JR, Walker RF, Riad-Fahmy D, Hall R. Salivary cortisol assays for assessing pituitary–adrenal reserve. Clin Endocrinol 1982;17:583–592.
25. Fitzgerald PA. Adrenal cortex physiology. In: Tierney Jr LM, McPhee J, Papadakis MA, eds. Current Medical Diagnosis and Treatment. Los Altos, CA: MA Lange Publishers, 1995.
26. Marz RB. Medical Nutrition from Marz, 2nd Edition. Portland, OR. Omni-Press, 1997.
27. Maffetone P. Complementary Sports Medicine. Champaign, IL: Human Kinetics, 1999.
28. Davis JM. Carbohydrates, branched-chain amino acids, and endurance: The central fatigue hypothesis. Int J Sport Nutr 1995;5:29–38.
29. Saito H, Yoshido Y, Takagi K. Effect of *Panax ginseng* root on exhaustive exercise in mice. Jpn J Pharmacol 1974;24:119–127.
30. Luo YM, Cheng XJ, Yuan WX. Effects of ginseng root saponins and ginsenoside Rb1 on immunity in cold water swim stress mice and rats. Chung Kuo Yao Li Hsueh Pao 1993;14:401–404.
31. Nishibe S, Kinoshita H, Takeda H, Okano G. Phenolic compounds from stem bark of *Acanthopanax senticosus* and their pharmacological effect in chronic swimming stressed rats. Chem Pharm Bull 1990;38:1763–1765.
32. Dionne JY. An overview of ginseng and other adaptogenic herbs. Int J Integrative Med 2000;(2):39–43.
33. Filaretov AA, Bogdanova TS, Mitushov MI, et al. Effect of adaptogens on the activity of the pituitary–adrenocortical system in rats. Biull Eksp Biol Med 1986;101:573–574.
34. Jeffries W. The present status of ACTH, cortisone, and related steroids in clinical medicine. N Eng J Med 1955;253:441–446.
35. Seriphos Web site. Online document at: www.lifeextensionvitamins.com/serphosser.html
36. Pagani M, Lucini D, Mela GS, Langewitz W, Malliani A. Sympathetic overactivity in subjects complaining of unexplained fatigue. Clin Sci 1994;87(6):655–661.
37. Urhausen A, Gabriel HH, Kindermann W. Impaired pituitary hormonal response to exhaustive exercise in overtrained endurance athletes. Med Sci Sports Exerc 1998;30(3):407–414.
38. DiGiovanna EL, Schiowitz S. An Osteopathic Approach to Diagnosis and Treatment. Philadelphia: JB Lippincott, 1997.

Chris D. Meletis, N.D., serves as the dean of naturopathic medicine/chief medical officer, National College of Naturopathic Medicine, Portland, Oregon. **Wayne A. Centrone, N.D., A.T.-C.,** is a second-year resident at the National College of Naturopathic Medicine and is also in private practice in Portland, Oregon.

To order reprints of this article, write to or call: Karen Ballen, *ALTERNATIVE & COMPLEMENTARY THERAPIES*, Mary Ann Liebert, Inc., 2 Madison Avenue, Larchmont, NY 10538-1961, (914) 834-3100.